STUDY PROPOSAL

EFFICACY OF AMODIAQUINE-ARTESUNATE AND ARTEMETHER-LUMEFANTRINE FOR THE TREATMENT OF UNCOMPLICATED CHILDHOOD *PLASMODIUM FALCIPARUM* MALARIA

MSF CATCHMENT AREA BARAKA, SOUTH KIVU, DRC

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LIST OF ABBREVIATIONS

A.	Anopheles
ACPR	Adequate clinical and parasitological response
ACT	Artemisinin Combination Therapy
ANC	Ante-Natal Care
ASAQ	Artesunate and Amodiaquine
CI	Confidence interval
CNDP	Congrès national pour la défense du peuple
CQ	Chloroquine
CRF	Case record form
DNDi	Drugs for Neglected Diseases Initiative
DRC	Democratic Republic of the Congo
ERB	Ethical Review Board
ETF	Early Treatment Failure
FARDC	Armed Forces of the Democratic Republic of the Congo
FDC	Fixed dose combination
FDLR	Democratic Forces for the Liberation of Rwanda
FTA	Fast Technology for Analysis (of nucleic acids)
h	hours
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
INGO	International Non-Governmental Organisation
IPD	Inpatient's department
IRS	Indoor Residual Spraying
ITT	Intention-to-treat
IV	Intravenous
KAP	Knowledge, Attitude and Practice
kg	kilogramme

LCF	Late Clinical Failure
LLIN	Long-Lasting Insecticide-treated bedNets
LPF	Late Parasitological Failure
LRA	Lord's Resistance Army
MoH	Ministry of Health
MSF	Médecins sans Frontières
MSF-OCA	Médecins sans Frontières – Operational Centre Amsterdam
MSF-OCB	Médecins sans Frontières – Operational Centre Brussels
MSF-OCBA	Médecins sans Frontières – Operational Centre Barcelona-Athens
NGO	Non-governmental agency
OPD	Outpatient's department
P.	Plasmodium
PCR	Polymerase Chain Reaction
PNLP	Programme National de Lutte Contre le Paludisme
RCD	Rally for Congolese Democracy
RDT	Rapid Diagnostic Test
SOP	Standard Operating Procedure
SP	Sulfadoxine-pyrimethamine
TB	Tuberculosis
UNSC	United Nations Security Council
WBC	White Blood Cells
WHO	World Health Organisation
WWARN	WorldWide Antimalarial Resistance Network

1 INTRODUCTION

Figure 1: Map of Democratic Republic of the Congo (DRC)[1]

1.1 HUMANITARIAN AND HEALTH SITUATION IN DRC

The long and brutal conflict in the DRC has caused massive suffering for civilians, with estimates of millions dead either directly or indirectly as a result of the fighting. There have been frequent reports of killing of civilians, destruction of property, widespread sexual violence and limited access to health care[4-7].

Despite a wealth of natural resources, Congo has one of the lowest per capita incomes in the world[2], in 2011 DRC ranked 187th (out of 187 countries) in the United Nations Development Programme's human development index, a composite measure of well-being through three components: health, education and income[3].

The DRC is considered a recurrent humanitarian crisis with acute health needs, limited access to humanitarian assistance and violations of basic rights and freedoms. In particular high morbidity and mortality are observed in areas affected by conflict where the institutional health system has been disrupted and few actors, whether Ministry of Health (MoH) or International Non-Governmental Organisations (INGOs), are providing basic healthcare services.

1.2 MEDECINS SANS FRONTIERES IN DRC

Médecins Sans Frontières-Operational Centre Amsterdam (MSF-OCA) has been working in the provinces of North Kivu and South Kivu since the early 1990s and Katanga since 2003. MSF-OCA operates 3 health programmes in Mweso (North Kivu), Katanga (DRC) and Baraka (South Kivu).

The North Kivu project in Mweso comprises primary Health Care with 3 supported Health Centres and Secondary Care in the Mweso Hospital.

The Katanga project is currently in an uncertain phase as MSF were in the process of closing the Shamwana project and opening the Bukama project. However due to security the population of Shamwana are displaced. In Shamwana MSF still support the Hospital in order to provide free secondary Health Care and more than 4 Health Centres. MSF ran an emergency malaria intervention in Bukama and Kinkondja from April 2012 to July 2012.

The South Kivu project in Baraka comprises primary health care with 3 supported health centres and secondary care in Baraka Hospital. Baraka Hospital is an official 160 bed general hospital, providing outpatient (OPD), inpatient (IPD-general, surgery, maternity), ante-natal care (ANC), tuberculosis (TB) and HIV treatment as well as nutritional care.

1.3 MALARIA IN DRC

Malaria is an important cause of morbidity and mortality and is considered a major public health problem in DRC, a high transmission country (≥1 per 1000 population)[4]. In 2011 DRC reported distributions of confirmed malaria cases of between 10 and ≥100 cases per 1000 population[4;5]. The disease accounts for an estimated 25–30% of child mortality, and is responsible for 68% of outpatient visits and 30% of hospital admissions averaged throughout the country[6]. In 2003, sentinel sites reported more than 4 million cases of malaria, which resulted in approximately 16500 deaths[6]. More than half of all estimated *P. falciparum* clinical cases and associated uncertainty occur in just 4 stable transmission countries (India, Nigeria, DRC, and Myanmar) where 1.405 billion people are at risk[7]

Malaria is holoendemic (perennial and intense malaria transmission) in most parts of DRC. *Plasmodium (P.) falciparum* is the predominant species responsible for 95% of malaria cases (5% *P. ovale and P. malariae*). The main vectors are *Anopheles (A.) gambiae and A. funestus* with secondary vectors being *A. moucheti* and *A. nili*[4]. Stable endemic transmission of malaria occurs all year round throughout DRC. Seasonal fluctuations in transmission intensity occur in the east and south of the country. The unstable context and population displacement may also affect transmission patterns.

1.4 CONTROL AND TREATMENT OF MALARIA IN DRC

In 2003, MSF adopted a strategy of introducing Artemsinin-based Combination Therapy (ACT) for the treatment of uncomplicated *P. falciparum* malaria in all MSF projects in malaria endemic areas in response to emerging evidence of its potential superiority to existing regimens and changes in WHO recommendations[8-11]. Artesunate-Amodiaquine (ASAQ) combination therapy was shown to be an effective treatment with a mean 28-day risk of treatment failure of less than 10%: 4.6% in Uganda[12], 1.5% in Congo[13], 6 to 9% in Tanzania[14] and 0% to 1.2% in Angola[15;16].

In 2001, the Ministry of Health of DRC produced a five year strategic plan to fight against malaria (2002-2006). The National Malaria Control Program (Programme National de Lutte contre le Paludisme (PNLP)) has two strategies, prevention, which is primarily the use of long-lasting insecticide-treated bednets (LLINs), and treatment. Artemsinin-based combination therapy (ACT)

with ASAQ, instead of Sulphadoxine/Pyrimethamine (SP), has been the national recommended treatment for uncomplicated malaria in DRC since 2004-2005.

As recommended by WHO, ACT drug efficacy should be monitored to detect potential drug resistance early and allow ministries of health to prepare rational treatment strategies and policies[11]. In 2009 MSF conducted an efficacy study of ASAQ versus Artemether-lumefantrine (Coartem®) in children aged between 6 and 59 months in Katanga Province, DRC. The outcome was that both ASAQ and Coartem® were highly effective with cure rates greater than 98% at 42 days. However, the authors recommended that surveillance of efficacy of artemesin-based therapies be undertaken in other provinces of DRC[17]. The findings were to a certain extent unsurprising. In 2009 a Cochrane review compared 9 trials of the same combinations and found no difference in the PCR-adjusted outcome at 28 days after treatment[18].

1.5 BACKGROUND

1.5.1 MALARIA IN MSF-OCA PROJECTS IN DRC

According to the OPD data in MSF-OCA projects in DRC for the year 2011, malaria represents one of the most common diagnoses, accounting for 20.5% of the total consultations during the year in Mweso, 30.4% in Baraka and 43.1% in Shamwana (overall 29% of all consultations). 46.7% of these malaria cases were diagnosed in children under the age of five years. In addition, according to the IPD data, 38.9% of all admissions were due to severe malaria.

Since 2010 confirmed malaria cases observed in MSF-OCA programmes have almost doubled and since 2009 a 5-fold increase in the number of malaria cases has been observed (Figure 2). In Shamwana (Katanga) and Baraka (South Kivu) the increase in malaria incidence has been particularly evident in under-5 year olds but similar in <5 and >=5 year olds in Mweso (North Kivu). However the population figures for Shamwana, Katanga are likely underestimated and hence the reported incidences should be treated with caution.

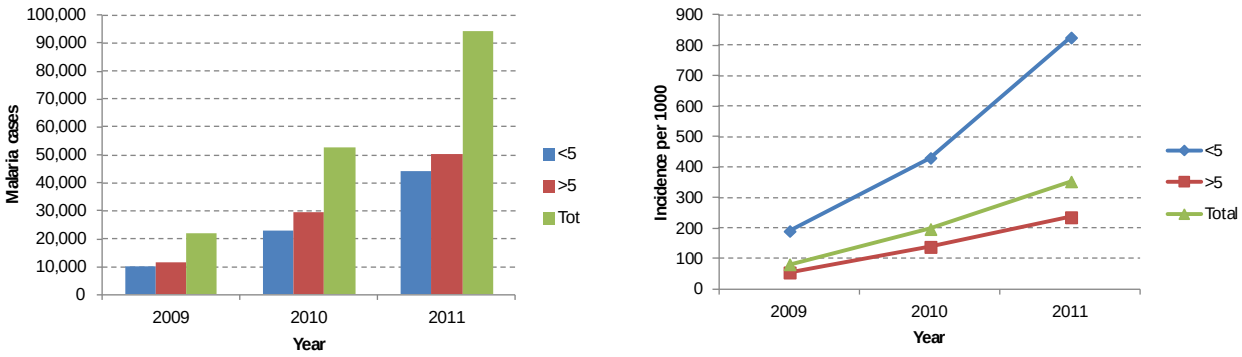

Figure 2: Confirmed malaria cases and estimated incidence in MSF-OCA programmes (Mweso, Baraka and Shamwana) in DRC, 2009-2011. The Katanga populations are likely underestimated hence the incidences should be treated with caution

This was an alarming increase in malaria incidence which cannot be explained by displacement of non-immune populations from non-endemic regions (mountains) to endemic malaria regions as happened with the IDP displacements in 2008 in Mweso. As the security situation in the 3 provinces

is volatile it means that there is frequent displacement over the last decade. As the steep increase is as of 2009, this is also not a plausible explanation.

In addition 2-3 recurrent malaria episodes have been observed in the same individuals, it is not known if these are treatment failures or re-infections.

1.5.2 MALARIA CONTROL INTERVENTIONS IN MSF-OCA PROJECTS IN DRC

Kashuga (Mweso) is characterised by poor housing and high population densities in villages and IDP camps situated in a swampy region of North Kivu. In response to the increase in malaria cases an indoor residual spraying (IRS) campaign was carried out in April 2010 and repeated every 4-6 months since then using alpha-cypermethrin (Fendona). The target coverage of 100% of dwellings in Kashuga was achieved. In addition LLINs were distributed to every household and canals were emptied in order to avoid stagnating water in the camp.

In Baraka MSF-OCA has been distributing LLINs in a targeted manner (ANC programmes and <5 year old malaria patients at OPDs). Although no IRS was carried out in Baraka, MSF-OCA's strategy of community health education targeted LLIN distribution and ACT treatment of confirmed malaria cases does not seem to be having an impact on malaria incidence. A similar pattern is observed in Katanga where despite similar control activities as Baraka, malaria incidence has increased since 2009.

1.6 RATIONALE FOR THE STUDY

In response to this recent increase in malaria cases in DRC, the recommendations for routine surveillance of ACT efficacy[11] and evidence of emerging artemisinin resistance in Asia[19] it has been deemed prudent to re-examine the question of the efficacy of ASAQ and Coartem® in DRC.

This study will complement several studies being undertaken in MSF sites in DRC to investigate potential causes of the increase in malaria cases. These include KAP surveys to study LLIN use, ACT adherence studies and a susceptibility study of the mosquito vectors to pyrethroids.

2 OBJECTIVES

2.1 STUDY HYPOTHESIS

The risk of recurrent parasitaemia after 42 days is not inferior in those receiving ASAQ compared to those receiving Coartem® (both of which have a high efficacy) The large increase in malaria cases in 2010 and 2011 in DRC is therefore not explained by poor ASAQ efficacy.

2.2 PRIMARY OBJECTIVES

To compare the *in vivo* efficacy of artesunate-amodiaquine (ASAQ) versus artemether-lumefantrine (Coartem®) in a population of children aged between 6 and 59 months suffering from uncomplicated *P. falciparum* malaria. This will be expressed as the PCR genotyping corrected rates of parasite clearance as a measure of efficacy at day 42 after initiation of anti-malarial therapy (the correction is for recrudescence versus re-infection). This will provide the MoH with evidence for the most appropriate choice of ACT for this region.

2.3 SECONDARY OBJECTIVES

- To measure the PCR uncorrected efficacy of both drugs at day 42 after treatment initiation
- To measure the PCR corrected and uncorrected efficacy of both drugs at days 14 and 28 after treatment initiation
- To calculate the proportion of early therapeutic failures, late clinical failures and late parasitological failures in a period of 42 days after treatment initiation
- To formulate recommendations and to enable the Ministry of Health to make informed decisions about whether the current national anti-malarial treatment guidelines should be updated.

3 MATERIALS AND METHODS

3.1 STUDY DESIGN

This will be an open-randomised non-inferiority study to test the hypothesis that the risk of recurrent parasitaemia after 42 days is not worse in the group receiving the Artesunate-Amodiaquine (ASAQ) regimen than in the group receiving the Artemether-Lumefantrine (Coartem®) regimen. Children with uncomplicated malaria meeting the inclusion criteria will be enrolled (after their parent/caretaker has given informed consent), treated on site with the drugs under evaluation and followed-up for a period of 42 days. Drugs will be given under direct supervision, either at the clinic or at home. Follow-up shall consist of a fixed schedule of clinical and laboratory examinations. Based on clinical and laboratory findings, children will be classified as therapeutic failures (early or late) or adequate responders.

The proportion of cases experiencing an in vivo therapeutic failure during the follow-up period will provide an estimate of the efficacy of the drug regimens. A Polymerase Chain Reaction (PCR) analysis will be carried out to differentiate true recrudescence due to treatment failure from episodes of re-infection. This proposal is compliant with the latest WHO recommendations for anti-malarial efficacy monitoring in high, medium or low transmission zones[11].

3.2 STUDY SITES

The study site will be the MSF catchment area of Baraka health centres, MSF-OCA Baraka, South Kivu, DRC.

Key security developments in 2012 in South Kivu included increasing clashes in the northern part of the province between Democratic Forces for the Liberation of Rwanda (FDLR) and Mai Mai Raia Mutomboki. Though this sometimes involved direct clashes between the groups it also frequently included attacks on / massacres of civilians perceived to be close to one of the sides.

Access for non-governmental agencies (NGOs) has been hampered by a number of security incidents that indicate the continued influence of fundamental ethnic mistrust (ongoing tribal clashes).

Figure 3: Map of South Kivu, DRC (with Baraka highlighted)[20]

3.3 STUDY POPULATION

The study population is children aged between 6 and 59 months with uncomplicated *P. falciparum* malaria. This age group was selected because it is considered the most vulnerable and is less likely to clear infections spontaneously compared to older children and adults. In hyper-endemic areas, they are the most at risk of dying from malaria.

3.4 DEFINITIONS

3.4.1 DEFINITION OF PARENT/CARETAKER

The parent/caretaker is defined as the household member who is aged ≥ 18 years who cares for the patient and can give accurate information on all demographic and health issues related to the patient and is present at the time of the survey.

3.5 INCLUSION AND EXCLUSION CRITERIA

A child will be eligible for study participation if s/he meets **all** of the following inclusion criteria:

- Age between 6 and 59 months
- Weight ≥ 5 Kg
- Slide-confirmed infection with *Plasmodium falciparum* only (no mixed infections)
- Asexual parasite density between 2000 and 200000/µl of blood
- Measured axillary temperature ≥ 37.5°C
- Ability to swallow oral medication

- High probability of respecting the follow-up visits (residence within 1 hour walking distance from the OPD, no upcoming travel plans, etc.)
- Informed consent from a parent or caretaker aged at least 18 years.

A child will be excluded from study participation if s/he meets **any** of the following exclusion criteria:

- General danger signs according to the WHO definition (Appendix 5.1.1)
- Signs of severe/complicated malaria according to the WHO definition (Appendix 5.1.2)
- Severe anaemia (haemoglobin < 5 g/dL)
- Known history of hypersensitivity to any of the study drugs
- Severe acute malnutrition (as defined by a weight-for-height below -3 Z-score and/or symmetrical oedemas involving at least the feet)
- Concomitant febrile illness due to causes other than malaria with the potential to confound study outcome (measles, acute lower tract respiratory infection, otitis media, tonsillitis, abscesses, severe diarrhoea with dehydration).
- Having received already a full course of the treatment (or one of the treatments) under study in the previous 28 days (as indicated by the parent/caretaker). Note that previous incomplete anti-malarial intake of treatments under study, or previous intake of anti-malarials not under study, are not exclusion criteria, but details of any such intake should be recorded carefully.
- History of hypersensitivity reactions or contra-indications to any medicines being tested.

3.6 SAMPLE SIZE

Recent studies had determined the 42-day risk of recurrent parasitaemia (treatment failure) in children to range from 0.9-6% with Coartem® therapy[14;17;21;22]. Therefore on the basis of an estimated risk of recurrent parasitaemia of 5%, we calculated that 120 patients per treatment arm would be needed to detect a difference in the risk of recurrent parasitaemia between treatment arms of no greater than 7% (one-sided type I error of 5%, 80% power)[23].

Assuming re-infections, undetermined PCR results or loss to follow-up occur in 20% of samples, the total estimated sample size of this study will be 288 children aged 6-59 months (144 per arm).

3.7 SCHEDULE OF ASSESSMENTS

Day 0 is the day of screening with clinical assessment, initial malaria blood smear, first haemoglobin measurement, pre-treatment capillary blood sample for PCR, enrolment and administration of first dose of drugs under study. On Day 1 and Day 2, treatment will continue and children will be re-assessed at the MSF clinic.

Children will return to the clinic on the following mandatory days: Day 3, 7, 14, 21, 28, 35 and 42. At each scheduled visit, a clinical examination and a blood smear will be performed. To encourage clinic attendance, small incentives will be offered such as soap, blankets and travel reimbursement. All children recruited to the study receive a long-lasting insecticide-treated bednet.

If children have to return to the clinic for unscheduled visits, at each time clinical and laboratory exams will be conducted as needed. In case of treatment failure at any day after day 7, a capillary blood sample for PCR will be collected.

Day of scheduled visit	Clinical assessment	Axillary temperature	Study doses	Malaria slide	PCR sample
Day 0 (Screening)	X	X	X	X	X
Day 1	X	X	X	X	
Day 2	X	X	X	X	
Day 3	X	X		X	
Day 7	X	X		X	
Day 14	X	X		X	X †
Day 21	X	X		X	X †
Day 28	X	X		X	X †
Day 35	X	X		X	X †
Day 42	X	X		X	X †
Unscheduled visits	X	X		X	X †

Table 1: Summary of follow-up schedule. †PCR sample to be collected on any day after day 7 in case of treatment failure

3.8 STUDY END POINTS

A study endpoint is the point at which a patient will no longer be followed-up within the context of the efficacy study. Valid study endpoints include treatment failure, completion of the follow-up period without treatment failure, loss to follow-up, withdrawal from study (voluntary and involuntary) and protocol violation[11].

3.8.1 EARLY TREATMENT FAILURE (ETF)

- Development of danger signs or severe malaria on Day 1, Day 2 or Day 3 in presence of parasitaemia , or
- Parasitaemia on Day 2 higher than Day 0 count irrespective of axillary temperature, or
- Parasitaemia on Day 3 with axillary temperature ≥ 37.5°C, or
- Parasitaemia on Day 3 ≥ 25% of day 0 count irrespective of axillary temperature.

3.8.2 LATE CLINICAL FAILURE (LCF)

- Development of danger signs or severe malaria on any day from Day 4 to Day 42 in the presence of parasitaemia (without previously meeting any of the criteria of ETF), or
- Presence of parasitaemia and axillary temperature ≥ 37.5°C on any day from Day 4 to Day 42 (without previously meeting any of the criteria of ETF)

3.8.3 LATE PARASITOLOGICAL FAILURE (LPF)

- Presence of parasitaemia and axillary temperature < 37.5°C on any day from Day 7 to Day 42 (without previously meeting any of the criteria of ETF or LCF)

3.8.4 ADEQUATE CLINICAL AND PARASITOLOGICAL RESPONSE (ACPR)

- Absence of parasitaemia on Day 42 irrespective of axillary temperature (without previously meeting any of the criteria of ETF, LCF or LPF)

3.8.5 NON ANALYSABLE ENDPOINTS

A patient's endpoint is not analysable if s/he meets any of the following criteria after his enrolment in the study. In non-inferiority studies, Intention-to-treat (ITT) analysis will often increase the risk of falsely claiming non-inferiority (type I error) so will not be carried out here[24].

3.8.5.1 Protocol violation:

- Failure to complete the full study treatment regimen, other than due to vomiting,
- Erroneous enrolment of the patient (not all inclusion/exclusion criteria respected),
- Intake of any anti-malarials or antibiotics with anti-malarial activity (cotrimoxazole, tetracycline except for eye ointment, doxycycline, erythromycin, clindamycin, azithromycin) as administered by a third party or through self-medication,
- Misclassification of the patient's endpoint (due to a laboratory or clinical error) leading to the unjustified administration of the rescue treatment,
- LCF or LPF with missing or undetermined PCR result.

3.8.5.2 Withdrawal:

- Severe malaria occurring on Day 0 after enrolment,
- Detection of a (mixed or mono-) infection with a non-falciparum species,
- Vomiting any study dose more than once,
- Side effects of the study drug severe enough that they require discontinuation of treatment,
- Hospitalisation for a reason other than malaria, rendering normal follow-up visits impossible.
- Withdrawal of consent

3.8.6 SAFETY ENDPOINTS

The occurrence of any adverse event will be documented. All patients will be asked routinely about previous symptoms and about symptoms that have emerged since the previous follow-up visit. When clinically indicated, patients will be evaluated and treated appropriately. All serious adverse events will be recorded on the case report form.

3.9 STUDY TREATMENTS

3.9.1 REGIMENS TESTED

- Artesunate-amodiaquine fixed dose combination, ASAQ FDC (artesunate-amodiaquine Winthrop® Sanofi Aventis) given as 1 tablet/day for 3 days:
    - Artesunate 25mg / amodiaquine 67.5mg: in children 5 to 8.9kg
    - Artesunate 50mg / amodiaquine 135mg: 1 tab/day in children 9 to 17.9kg
    - Artesunate 100mg / amodiaquine 270mg: 1 tab/day in children 18 to 34.9kg
- Artemether 20mg / lumefantrine 120mg co-formulated tablets (Coartem®, Novartis) given as six twice-daily doses over three days:
    - 1 tab/dose for children 5 to 14.9kg (total 6 tabs)
    - 2 tabs/dose for children 15 to 24.9kg (total 12 tabs)
    - 2 tabs/dose for weight 15-24.9kg (total 12 tabs)
    - 3 tabs/dose for weight 25-34.9 Kg (total 18 tabs)

    The second dose of Coartem® will be given 8 hours (h) after the first dose, given at enrolment. The following doses will be given 24h, 36h, 48h and 60h after the first dose. Patients will be given a glass of milk or fatty food, or encouraged to breastfeed before each dose is taken.

Drugs under study will come from the same batch. All study doses will be supervised. Patients will be directly observed following intake for 30 minutes. If vomiting occurs, a repeat dose will be administered. If the repeated dose is also vomited, the child will be withdrawn from the study, and rescue treatment will be initiated.

In order to administer the evening doses of Coartem®, a home visitor/village health worker will go to the patient's home 8h, 32h and 56h after the first dose. Thus recruitment to this study will only take place in the OPD before 12pm

3.9.2 CONCOMITANT TREATMENT

Fever over 38°C can be treated with paracetamol or acetaminophen, one dose of 20 mg/kg of paracetamol, followed with 15 mg/kg at 4 to 6 hourly intervals for home treatment. Tepid sponging can be used to reduce fever before drug intake.

Adverse events requiring treatment can be treated according to local practice. If there is a clinical indication for any additional medication during the course of the study, including medication given to treat an adverse event related to the study medicine, the name of the medicine, the dosage and the date and time of administration must be recorded on the case report form. Additional prescriptions may be given on enrolment or during follow-up for conditions other than malaria, although antibiotics with anti-malarial activity (cotrimoxazole, tetracycline except for eye ointment, doxycycline, erythromycin, clindamycin, azithromycin) will not be prescribed unless no equally effective alternatives are available. Any such prescriptions will be noted carefully.

The use of herbal remedies during the study should be avoided, and participants should be encouraged to return to the study site for treatment if they feel unwell. If any herbal remedies are taken during the study, this should be captured on the case report form, under 'study medication administration'.

Haematinics (like ferrous sulphate and folic acid) will be prescribed to ameliorate anaemia according to WHO[25] if necessary.

3.9.3 RESCUE TREATMENT

Rescue treatment for malaria shall be initiated immediately according to WHO guidelines[25] for the following cases:

- Progression to severe malaria on Day 0 after enrolment
- Vomiting any study dose more than once
- Early treatment failure
- Late clinical failure
- Late parasitological failure
- Detection during follow-up of a non-P. *falciparum* (mixed or mono-) infection, irrespective of fever

Rescue treatment shall consist of six-dose Coartem® for 3 days for the children that had received ASAQ as study-treatment or ASAQ for the children that had received Coartem® as study-treatment.

- In cases of severe malaria, rescue treatment will be intravenous artesunate at a dose of 2.4 mg/kg at 0, 12 and 24 hours, then once every 24 hrs until the patient can take oral therapy (This will be followed by 3-days full course of ACT)

Non-*falciparum* species detected during follow up should be treated with Chloroquine for 3 days in the case of infection with *P. vivax* or *P. ovale*.

Once rescue treatment is initiated, normal study follow-up ends for the patient, as an endpoint has been reached. However, patients who receive rescue treatment will be asked to return to the study clinic at least once, so that the study team can verify whether the treatment has been effective.

3.10 STUDY PROCEDURE

3.10.1 SCREENING AND ENROLMENT (DAY 0)

All children aged between 6 and 59 months presenting at the Baraka Health clinic with fever or a history of fever and positive RDT and with no danger signs (Appendix 5.1.1) will be sent to the study clinic for screening.

All patients entering the screening process will be assigned a consecutive screening number. The screening form (Appendix 5.2) will be used to record the general information and the clinical observations of each patient being screened. Each patient will be assessed again for danger signs and signs of severe malaria. Middle-upper arm circumference (MUAC) will then be used as a screening tool for malnutrition. An initial clinical assessment will be done including inclusion and exclusion criteria, previous treatment history (including ingestion of any anti-malarial drugs), clinical examination and weight-for-height on children with MUAC <125 mm.

Care will be taken to detect early signs of febrile diseases other than malaria, as their presence will necessitate exclusion from the study. These patients will not be enrolled but should be treated for both malaria (if they have parasitaemia) and the other infection, as appropriate.

If the patient meets the clinical inclusion criteria, s/he will be examined for blood inclusion criteria (*P. Falciparum* mono-infection, parasite density and haemoglobin levels). Thick and thin malaria smears will be taken on the same slide in duplicate and one smear will be stained. At the same time, a capillary blood sample will be taken on Fast Technology for Analysis (of nucleic acids) or FTA Cards for PCR analysis. The patient will wait for the thick smear result.

If all inclusion criteria are met, the patient will be invited to enrol in the study. The study purpose will be explained to the parent/caretaker who must be aged 18 years or above and a written informed consent will be requested (Appendix 5.4). All parents/caretakers will receive an information sheet containing the study purpose and study team contact details (Appendix).

If the parent/caretaker consents to include the child in the study, a unique patient identification number will be assigned to the child and a wrist band with the identification number will be given. Administrative data will be recorded (name of child and parent/caretaker, gender, age, address and directions) on a Case Record Form (Appendix 5.5). An appointment schedule will be clearly explained and a follow-up card marked with the unique patient identification number will be handed out.

Each unique patient identification number will be randomised to a treatment regimen before the study starts and this information will be contained in sealed envelopes. The first dose of the study drug will be dispensed at the health clinic (for children who cannot swallow, Coartem® tablets will be dissolved, and ASAQ tablets will be crushed in minimal amounts of water and dispensed by help of a syringe or dropper). Intake will be observed for 30 minutes. If the child vomits, a resting period of 15 minutes will be observed before attempting a repeat dose. Any concomitant prescriptions will be collected at the designated pharmacy and care will be taken to ensure that the instructions on home treatment are clear to the parent/caretaker.

Before being sent home, the patient's parent/caretaker will repeatedly be advised to bring him/her back the study clinic at any time if symptoms persist or worsen.

In order to administer the evening doses of Coartem®, a home visitor/village health worker will go to the patient's home 8h, 32h and 56h after the first dose. Thus recruitment to this study will only take place in the OPD before 12pm.

3.10.2 Follow-up (day 1 to Day42)

On Days 1 and 2, study drug treatment is continued; the fourth (Day 1) and sixth (Day 2) Coartem® doses will be administered at home as described above by a home visitor. However all patients will return to the MSF clinic for a clinical assessment (including measurement of axillary temperature) and parasitological examination by malaria slide. All ASAQ and the 3rd and 5th Coartem® doses will be observed during these clinic visits.

On Days 3, 7, 14, 21, 28, 35 and 42, all patients will return to the MSF clinic for a clinical assessment (including axilliary temperature) and blood smear examination.

If treatment failure is observed (ETF, LCF or LPF) rescue treatment will be initiated. For LCF or LPF occurring after Day 7 (since if there is a re-infection it will not lead to clinical symptoms before day 7

so we can assume it's a recrudescence) a second blood sample will be collected on FTA cards for PCR analysis.

For unscheduled visits by patients, a clinical assessment will be performed, and a malaria slide (and blood sample for PCR in case of treatment failure) may be taken if there are signs and symptoms of possible malaria.

Before being sent home after each visit, the parent/caretaker will be advised to bring the patient back to the MSF clinic at any time in case of any illness. In case of emergency outside of working hours, parents/caretakers will be advised to bring their appointment card and to inform emergency staff of their child's inclusion in the study.

Instructions will be given to emergency staff to report all information concerning the event to the study coordinator the next morning.

Attempts to trace children who fail to return for scheduled visits will be made immediately by a home visitor to minimise loss to follow-up.

Patients who fail to return on days 1 and 2 and miss one dose of the treatment will be withdrawn from the study. After day 3, patients who fail to return on day 7 but are present on day 6 or 8 (likewise days 13/15, days 20/22, days 27/29, days 34/36 and days 41/43) may still be included in the analysis.

3.10.3 MEASUREMENT TECHNIQUES

- Weight will be measured to the nearest 100 g on a hanging scale (Salter) properly calibrated with only undergarments kept on the child.
- Height will be measured on a wooden height board, by asking the child to stand if s/he is > 85 cm, or by laying the child horizontally if s/he is < 85 cm.
- MUAC will be measured on the left arm, at the mid-point between the elbow and the shoulder and will be recorded to the nearest mm.
- Oedema will be assessed by 3 second thumb pressure on the dorsal surface of both feet.
- Axillary temperature will be measured with a calibrated digital thermometer graduated in Celsius, with a precision of 0.1°C. If the result is <36.0°C, the measurement will be repeated.

3.11 LABORATORY TECHNIQUES

3.11.1 MALARIA SLIDES

Thick and thin smears will be prepared on the same slide and stained in 10% Giemsa solution (pH 7.2) for 10-15 minutes. All smears must be read to 100 fields before they can be declared negative. Species will be confirmed on the thin smear. Quantification of *P. falciparum* asexual parasitaemia on the thick smear will be performed according to the WHO protocol[26]. Parasites will be counted against at least 200 white blood cells/leucocytes (WBC), and the parasite density (expressed in parasites per µL of blood) will be calculated assuming a normal level of 8000 WBC/µL:

Parasite density (/µL) = number of parasites counted x 8000 / number of WBC counted

If 500 parasites are counted before reaching 200 WBC, the counting will be stopped at the end of that field and the parasitaemia will be calculated with the above formula. If less than 10 parasites are counted after 200 WBC, the counting will be extended to 500 white cells.

Presence or absence of *P. falciparum* gametocytes does not influence endpoint classification, but will be recorded carefully and systematically. If a smear contains gametocytes but not trophozoites (asexual parasites) it will be considered negative.

Two qualified microscopists will read all the slides independently, and parasite densities will be calculated by averaging the two counts. Blood smears with discordant results (differences between the two microscopists in species diagnosis, in parasite density of >50% or in the presence of parasites) will be re-examined by a third, independent microscopist and parasite density will be calculated by averaging the two closest counts.

All blood smears will be destroyed once data analysis is complete.

3.11.2 HAEMOGLOBIN MEASUREMENT

The HemoCue B-Haemoglobin analyser (Ängelholm, Sweden) apparatus will be used to measure haemoglobin on Day 0 or any other day if clinically warranted.

3.11.3 PCR GENOTYPING

PCR genotyping analysis will be performed in order to distinguish true recrudescence (same parasite strain) from a newly acquired infection (different parasite strain). Capillary blood samples for PCR will be collected for all patients at enrolment and during follow-up in case of LCF or LPF after Day 7.

2-3 drops of capillary blood will be collected on FTA cards, stored individually in zip-lock bags with desiccant, and kept away from humidity, excessive heat and light.

The genotyping will be performed at the department of Medical Microbiology, at the Academic Medical Center (Amsterdam, The Netherlands), under the supervision of Prof. Dr Tom van Gool. A material transfer agreement will be signed. The genotyping procedure will be based on comparison of the two-locus genotype resulting from expression of the *P. falciparum* MSP-1 and MSP-2 gene alleles in pre- (enrolment) and post-treatment (failure) samples[27]. Pre- and post-treatment pairs with similar genotype will be classified as recrudescence (true failure), and pairs with different genotype will be classified as re-infection.

3.11.4 QUALITY CONTROL OF MALARIA DIAGNOSIS

Before the study starts, correct laboratory procedures, such as staining technique, staining time, dilution and data reporting will be established. A blinded re-reading of routine malaria slides (of which at least 20 will be positive) will be performed and discordances reviewed.

An external quality control, with a reference parasitological laboratory, is envisaged at the end of the study on a random sample of 20 positives slides collected between Day 0 and Day 42.

3.11.5 MOLECULAR MARKERS FOR ANTI-MALARIAL DRUG RESISTANCE

Currently there are no clear molecular markers associated with decreased susceptibility to ACTs. Therefore we do not anticipate at this moment to study molecular markers of ACT resistance. However a region of chromosome 13 on the *P. falciparum* genome that is linked to decreased parasite clearance rates in response to ACTs has been identified[28]. If putative markers of artemisinin resistance are identified in the next 5 years the FTA cards from this study should be made available to the World Wide Antimalarial Resistance Network (WWARN) for analysis. Permission to store the FTA cards at -70^{o}C at the Amsterdam Medical Centre, The Netherlands for 5 years after termination of the study, and their use for determination of molecular markers of resistance will therefore be requested in the informed consent forms.

3.12 DATA ANALYSIS

3.12.1 DATA MANAGEMENT

All case record forms (CRF) will be double-entered daily using EpiData 3.1 software (Odense, Denmark), merged (with verification of inconsistencies) and analysed using Stata version 10 (Stata Corporation, USA) statistical software. An interim analysis of early treatment failure will be carried out once all the participants have reached day 3 and their blood smear results are available. This is to assess at an early stage whether the non-inferiority hypothesis regarding early treatment failure should be rejected. At the end of the study analysis, all CRFs and other source data (consent forms, laboratory registers, screening forms, etc) will be stored securely at the capital level. Data will also be submitted to the WWARN database for the international monitoring of anti-malarial drug resistance. A copy of CRFs will also be stored for at least 5 years at MSF-OCA in Amsterdam. The principal investigator is responsible for keeping all screening forms, the case report form and the completed subject identification code list in a secure location.

3.12.2 ANALYSIS PLAN

- Description of the study : numbers of patients screened, number of patients with a *P. falciparum* infection, number of patients infected with other *Plasmodium* species, number of patients excluded (and, if possible, reasons for non-eligibility), numbers of included, randomised and analysable patients

- Validity of the study : results on internal and external laboratory quality control, % of overall non analysable patients and % of overall non analysable patients and % loss to follow-up

- Characteristics of included patients: age, sex, weight-for-height, previous intake of anti-malarials, axillary temperature, parasite density, gametocyte carriage, haemoglobin. Chi-square test will be performed to test the adequacy of randomisation.

- Description of study endpoints: numbers of ETF, LCF, LPF and ACPR at Day 42. Similar outcomes would be assessed at Day 28 for comparison with Day 42 efficacy.

- Adverse events: the proportion of adverse events and serious adverse events in all the patients included in the study for each drug;

- PCR genotyping analysis: number of samples analysed, number of recrudescence episodes and re-infections, number of mixed and undetermined results

- Efficacy estimates: Kaplan-Meier survival analysis methods will be used with and without genotyping adjustment. Patients withdrawn, lost to follow-up or with re-infections are censored from the analysis on that day. Patients with a recurrence of parasitaemia, but with missing or undetermined PCR results should be censored on the last visit when the malaria smear was found to be negative (as it is known that the patient was ‘cured’ at that point).

- Data analysis: Per-protocol analysis followed by a survival analysis using the Kaplan-Meier method. In addition to the reasons for withdrawal listed above, patients will be considered withdrawn from the analysis if the PCR results are unclassifiable or if the results of PCR indicate that the failure is due to re-infection with *P. vivax. P. malariae* or *P. ovale*. The cumulative incidence of success and failure rates at day 28/42, PCR-uncorrected and PCR-

corrected for each drug; and the proportion of early treatment failure, late clinical failure, late parasitological failure and adequate clinical and parasitological response at day 28/42, with 95% confidence intervals, PCR-uncorrected and PCR-corrected will be calculated

3.12.3 STUDY REPORT

At the end of the study, the principal investigator will submit a report on the study and its main outcome. This report will be shared with the national malaria control programme and the Ministry of Health.

The study results will be presented at appropriate scientific meetings and potentially published in a peer-reviewed journal. Data will also be submitted to the WWARN database for the international monitoring of anti-malarial drug resistance.

Study results will be shared with the community leaders, and in patient meetings. Results will be displayed in lay-language in the health clinic.

3.13 ETHICAL CONSIDERATIONS

3.13.1 AUTHORISATION AND COLLABORATIONS

The study will conducted in accordance with the World Health Assembly of 1975 concerning ethical aspects in human tests, and with the Helsinki declaration.

The study proposal will be submitted to the Ethics Review Board of MSF. It will also be submitted to the DRC ethical review process for approval.

3.13.2 INFORMED CONSENT

Patients will be included in the study only if the parent/caretaker gives written informed consent. The information sheet and informed consent will be available in French and translated into the local language. They will be read entirely to the parent/caretaker. Details about the study and its benefits and potential risks will be explained. Once any questions have been answered, a signature will be requested on the informed consent document (Appendix 5.4). If the patient is illiterate, a literate witness will be asked sign; if possible, the signatory will be selected by the participant and will have no connection to the research team.

3.13.3 CONFIDENTIALITY

All information on patients will remain confidential and be shared only amongst the study team.

3.13.4 HEALTH SERVICES

Free health care throughout follow-up for any illness related or not to malaria will be provided to all patients invited to participate in the study regardless of whether they consented and regardless of treatment outcome; this includes any expenses related to health clinic admission and to adverse medicine reactions, if required.

Any person who decides not to participate or who cannot be enrolled into the study because he or she does not meet the criteria will be referred to the health facility staff. Such people will be treated and

followed-up according to the standard of care established by the Ministry of Health and MSF in the health clinic.

If a patient is withdrawn from the study before s/he has completed the full course of the treatment, the physician must make all necessary arrangements to provide the patient with the full dose of the medicine being tested or with a full course of anti-malarial drugs.

3.13.5 INDUCEMENT

Subjects shall be reimbursed for their transport to attend all visits to the health centre. LLINs will be provided to all participants. To encourage clinic attendance, small incentives will be offered such as soap, blankets.

3.13.6 RISKS AND BENEFITS

Risks for the study participants are minimal and linked to discomfort of frequent finger-pricks but which carry minimal risks of infection. Furthermore, study participants and their parent/guardian will be investing a significant amount of time to attend follow-up visits. Benefits for the study participants include a close clinical follow-up both during the initial treatment, as well as during the next weeks, which should reduce the risk of morbidity and mortality in general and linked to malaria infection

4 IMPLEMENTATION OF THE STUDY

4.1 HUMAN RESOURCES

The study team will work full time (7 days a week) through a rotating schedule, but enrolments will not take place on Sundays. The team will consist of:

- One medical doctor: overall study coordinator and in charge of clinical assessment, diagnoses, case record forms, consent-taking and data entry. This person is also responsible for presentation of the study proposal to the ethics committee of DRC
- One nurse, in charge of clinical assessment at enrolment, explaining of the study objectives, follow-up of patients and data collection
- Two nursing aides: in charge of weight-for-height and temperature measurements, treatment administration and supervision and recording complete patient information
- One senior laboratory technician: in charge of the organization and supervision of the laboratory work and quality control of slide reading
- Two laboratory technicians: in charge of preparing and reading slides, haemoglobin measurement and PCR sampling.
- Four home visitors:, checking the appointment schedule, administration at home of the evening Coartem® doses and tracing children who have missed follow-up appointments
- One epidemiologist in charge of writing the study standard operating procedures (SOPs), helping to set up the study in the field, remote supervision, final analysis and contributing to report writing.

4.2 TRAINING OF STUDY TEAMS AND PILOT SURVEYS

Good training of the study team is essential to ensure good quality of the data collection, and the validity of the results.

One day of training (if needed, additional day(s) of training will be added) will be given to all clinical staff and home visitors to familiarise them with the background of the study, the SOPs and their specific roles. Training will consist of an intensive review of the SOPs and role-plays. A hard copy of the appropriate study guideline will be provided to all study team members.

During the training it will be stressed that the caretaker/parent of the patient should not be influenced in any way; the caretaker/parent of the patient should feel comfortable to ask questions and voice their concerns at any point.

The training will be completed with a pilot study. The pilot study will allow for the testing and possible adaptation of the SOPs, study forms and informed consent under field conditions.

4.3 SUPERVISION

On Day-0, the study supervisor should ensure that sufficiently detailed information on the patient's address is collected to maximise the chances of locating the household of all study patients.

The study supervisor should supervise all teams at each stage of the study equally, and as much as possible, for the whole duration of the study. It is important attend clinical assessments, observe parasitological examinations and if possible observe some of the treatment doses.

At the end of each day, the study supervisor will review in detail each data collection form with the appropriate team, to ensure it was filled-in completely and correctly. Any unclear answers need to be identified and discussed with the team in order to avoid this as much as possible in the following days.

4.4 TIMEFRAME AND TIMING

It is recommended that the assessment should be carried out if possible in the period of high malaria incidence to ensure achievement of the sample size. The field part of the study falls exactly within this peak period (Table 2).

Activity	Time	Days needed
Preparation		
Writing and finalizing of the proposal	Mar 2013	
Ethics Review Board of MSF and DRC	Apr-Jun 2013	
Discussion with responsible persons to prepare field component	Jul 2013	
Field study	Aug 2013	
Preparation phase (recruitment HR, information to health staff, etc)	Aug 2013	3 days
Training study team	Aug 2013	1-2 days
Testing of SOPs	Aug 2013	1 day
Final adaptation of SOPS, final preparations, photocopies, etc.	Aug 2013	2 days
Data collection and daily data entry	Aug-Nov 2013	12-15 weeks
Completion		
Analysis of results	Dec 2013	5 days
Report writing	Dec 2013	10 days

Table 2: Estimation of days needed and planned timeframe for efficacy study

4.5 LOGISTICS AND SUPPLIES

The MSF field team is responsible for administrative support at the field level during study preparation and implementation including:

- Human resources support, e.g. hiring and payment of key clinical and field staff and supervision of local staff during the study
- Logistic support e.g. sufficient cars including drivers, communication tools for the teams, supplies and photocopies of forms, information sheets, written consents and guidelines

5 APPENDIX

5.1 DANGER SIGNS AND DEFINITION OF SEVERE MALARIA

5.1.1 GENERAL DANGER SIGNS

- Inability to drink or breastfeed
- Vomiting everything
- Recent history of convulsions
- Lethargy or unconsciousness
- Inability to sit or stand up

5.1.2 SEVERE MANIFESTATIONS OF P. FALCIPARUM *IN CHILDREN*

Prognostic value	**Clinical manifestations**	**Frequency**
+	Prostration	+++
+++	Impaired consciousness	+++
+++	Respiratory distress (acidotic breathing)	+++
+	Multiple convulsions	+++
+++	Circulatory collapse	+
+++	Pulmonary oedema (radiological)	+/-
+++	Abnormal bleeding	+/-
++	Jaundice	+
+	Haemoglobinuria	+/-
Laboratory findings		
+	Severe anaemia	+++
+++	Hypoglycaemia	+++
+++	Acidosis	+++
+++	Hyperlactataemia	+++
+/-	Hyperparasitaemia	++
++	Renal impairment	+

On a scale from + to +++; +/- indicates infrequent occurrence

Table 3: Signs of severe malaria[25]

5.2 SCREENING FORM

Date of visit (dd/*mm)* :				Screening number:	
Full name of the child:				Age (*months)* :	
Name of parent/caretaker:				Sex : □ M □ F	
Address :				Weight (*kg*) :	
				Height (cm*) :*	
Checklist of selection criteria: circle the correct answer					
Severe malaria					
Unable to drink or breastfeed	Yes	No	Vomiting everything	Yes	No
Unable to sit or stand	Yes	No	Lethargic or unconscious	Yes	No
Any other signs of severe malaria	Yes	No	Recent history of convulsions	Yes	No
If yes, specify other sign:					
If one of the above answers is "yes", the child is not eligible					
Severe malnutrition					
Weight-for-height <70%	Yes	No	Bilateral oedema	Yes	No
If one of the above answers is "yes", the child is not eligible					
Inclusion criteria					
Age 6-59 months	Yes	No	P. Falciparum mono-infection	Yes	No
Weight >=5kg	Yes	No	Parasite density 2 000-200 000/ul	Yes	No
Axillary temperature >= 37.5^{o}C	Yes	No	haemoglobin >= 5g/dl	Yes	No
No serious concomitant febrile illness	Yes	No	Lives close < 1h	Yes	No
No history of allergy to drugs under study	Yes	No	No anti-malarial drugs in the last 28 days	Yes	No
If all of the above answers are "yes", the child is eligible. Ask for informed consent.					
Written consent of parent/caretaker	Yes	No			
Inclusion in the study	Yes	No			
If the child is included:					
Identification number		Treatment allocation		1	2
Detailed address:					
IF the child is not included, specify the reasons for non inclusion					

5.3 PATIENT INFORMATION SHEET

Efficacy of Artesunate-Amodiaquine and Artemether-Lumefantrine for the treatment of uncomplicated childhood *Plasmodium falciparum* malaria in Baraka, South Kivu Province, DRC, 2013

Dear parent/guardian,

As you probably know, malaria is one of the main health problems in Democratic Republic of Congo. This study is comparing the currently used treatment (artesunate and amodiaquine) to another treatment (Coartem®). The results of this study will be useful for the community of Baraka, since they can result in better medicines being used to cure malaria here.

In this study, we are treating children who have malaria with one of the two treatments we told you about (chance will decide what treatment your child receives). We are following them up, during 6 weeks, to see how well the treatment has worked. The treatments we use have already been tested in other areas of the world, and proven to be as safe as the malaria treatments you're used to.

If you agree to let your child take part in this study, we will treat your child here today, tomorrow and the following day (but your child doesn't need to spend the night). However, you will also have to bring your child back the day after the treatment has finished, and six more times over the 6 weeks, so that we can measure your child's response to the treatment, and see how he/she is doing. If you think that you will not be able to bring your child back, let us know now. Your child will still receive treatment as usual, but he/she cannot be included in this study.

If you accept that your child is included in the study, at each visit, your child will have a full medical examination and small drops of blood will be taken from his/her finger to see if there are still malaria parasites in the blood. Blood will be also collected on filter paper for a special test to be done in Amsterdam (The Netherlands). These tests will tell us more about the parasite in your blood and the action of the medicine on the parasite.

You don't have to agree to let your child participate; it's up to you to decide. Also, you may stop bringing your child to the study at any time and for any reason. Your decision to stop bringing your child for the study will not affect the care we offer to you or your child for any medical reason. He/she will receive the best treatment available locally. And if he (she) needs to be treated in hospital, the expenses for this will be paid for by MSF.

Benefits from taking part in this study are close follow-up of your child. Thus we will be able to treat him/her right away in case malaria comes back, or another health problem appears. During the study, it will be possible that your child has side effects due to the treatment (vomiting, diarrhoea, etc.).

Note that your child must return to the clinic for the planned visits even if he/she is not sick. This is very important. At any time during the study, even outside the schedule of appointments, if your child feels sick, you should bring him/her back for a check up, even on weekends. It doesn't cost anything.

If you accept that your child is included in the study, at each visit, your child will have a full medical examination and small drops of blood will be taken from his/her finger to see if there are still malaria parasites in the blood. Blood will be also collected on filter paper and shipped to a laboratory in Amsterdam (Holland) for 2 special tests. These tests will tell us more about the parasite in your blood and the action of the medicine on the parasite.

In addition, there is a possibility that a new type of test be available in the coming years, which will help understand the effects of malaria treatment much better. In order to be able to contribute to more knowledge in this area, we would like to request your permission to keep the remaining blood for 5 more years after end of this study. If you do not agree with this, your blood will be discarded immediately after the end of the study. If you do agree your blood samples will be destroyed after 5 years.

The information we collect will be treated confidentially. It will be seen only by the study team, will be entered in a computer database without the name of patient and destroyed after 5 years. It will be used to decide on which malaria treatment should be used here in the future. The results of the study may be published in a medical journal, but be sure that no name will be shown.

Do you have any questions about the study? Please ask all the questions that you feel like asking. Note that you can change our minds at any time and stop bringing your child to the study.

If you accept to participate, please sign the form below.

If you have any questions/complaints, please contact the coordinator of the study at Baraka health clinic (*physical address and phone number will be given later on*)

5.4 WRITTEN CONSENT FORM

Efficacy of Artesunate-Amodiaquine and Artemether-Lumefantrine for the treatment of uncomplicated childhood *Plasmodium falciparum* malaria in Baraka, South Kivu Province, DRC, 2013

Full name of patient:

Parent's/guardian's name:

The above information has been read to me, or I have read it. I have been able to ask questions about the study. I voluntarily consent to my child's participation in this study and the storage of his/her blood samples for the next 5 years and I understand that I can withdraw my child any time from the study.

Date: / /

Signature (or fingerprint) of the parent/guardian

The above information has been read to me, or I have read it. I have been able to ask questions about the study. I voluntarily consent to my child's participation in this study BUT NOT the storage of his/her blood samples for the next 5 years and I understand that I can withdraw my child any time from the study.

Date: / /

Signature (or fingerprint) of the parent/guardian

Name of witness:

Signature of witness (if parent/guardian is illiterate)

Name of responsible staff member:

Signature of responsible staff member

NB: A copy is given to the parent/guardian

5.5 CASE RECORD FORM

Date of inclusion (*dd/mm)*:		**Identification number:**	
Name of the child:		**Age (*months)*:**	**Sex:** □ **M** □ **F**
Name of parent/caretaker:			
Address :			
Weight (*kg*):	**Treatment:** □ **ASAQ** □ **COARTEM**	**Total dose of drug (*mg):***	

Day:	**D0**	**D1**	**D2**	**D3**	**Other dates D4-D6**		**D7**	**Other dates: D8-D13**		**D14**
Date *(dd/mm)*										
General danger signs *(Yes/No)*										
Severe signs of malaria *(Yes/No)*										
Other severe diseases *(Yes/No)*										
Fever in the last 24h *(Yes/No)*										
Self-medication for malaria (*Yes/No)*										
Axillary temperature										
Haemoglobin										
Parasitaemia (*µl*)										
Species of Plasmodium										
Number of tablets given										
Alternative treatment (*Yes/No)*										
Other treatments										
PCR (*Yes/No)*										
Observations										

Day:	D21	Other dates D22-D27		D28	Other dates D29-D34		D35	Other dates D36-D41		D42
Date *(dd/mm)*										
General danger signs *(Yes/No)*										
Severe signs of malaria *(Yes/No)*										
Other severe diseases *(Yes/No)*										
Fever in the last 24h *(Yes/No)*										
Self-medication for malaria (*Yes/No)*										
Axillary temperature										
Haemoglobin										
Parasitaemia (*µl*)										
Species of Plasmodium										
Alternative treatment (*Yes/No)*										
Other treatments										
PCR (*Yes/No)*										
Observations										

Classification : give the date and the reason
1. Follow-up: □
2. Exclusion: □
3. Early treatment failure: □
4. Late clinical failure: □
5. Late parasitological failure: □

6 REFERENCES